(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 May 2001 (31.05.2001)

PCT

(10) International Publicati n Number
WO 01/37814 A1

(51) International Patent Classification[7]: A61K 9/24, 31/465

(21) International Application Number: PCT/GB00/04428

(22) International Filing Date:
22 November 2000 (22.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9927525.7 23 November 1999 (23.11.1999) GB
0021645.7 4 September 2000 (04.09.2000) GB

(71) Applicant *(for all designated States except US)*: **ROBERT GORDON UNIVERSITY** [GB/GB]; Schoolhill, Aberdeen AB10 1FR (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **PARK, Calum** [GB/GB]; Top Floor Flat, 8 Bon Accord Terrace, Aberdeen AB11 6DP (GB). **MUNDAY, Dale** [GB/GB]; 2A Hopetoun Grange, Bucksburn, Aberdeen AB21 9RB (GB). **BAIN, David, Francis** [GB/GB]; 126 Picktillum Place, Aberdeen AB25 3AW (GB). **SHAKOOR, Omar** [GB/GB]; 65 Rose Street, Aberdeen AB10 1UH (GB).

(74) Agent: **MURGITROYD & COMPANY**; 373 Scotland Street, Glasgow G5 8QA (GB).

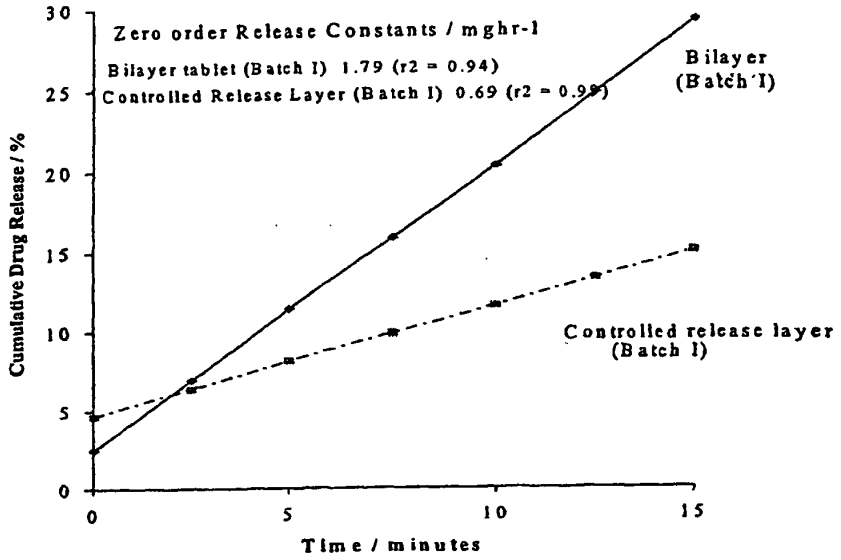
(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BILAYERED BUCCAL TABLETS COMPRISING NICOTINE



(57) Abstract: A method of delivering substance, e.g. a drug, to a subject comprises attaching a tablet or other dosage form to a buccal mucosa, where the dosage form is adapted to release the substance in a multiphasic manner, typically with an initial burst release of substance followed by controlled release over a longer period. The substance is typically nicotine.

WO 01/37814 A1

BILAYERED BUCCAL TABLETS COMPRISING NICOTINE

This invention relates to the delivery of substances such as bio-active agents and pharmaceuticals to the body. In a preferred embodiment the invention concerns the delivery of nicotine to the buccal area.

Nicotine replacement therapy (NRT) is a frequent component of strategies to help smokers stop smoking. Present NRT delivery systems include chewing gum and transdermal patches which release the drug over a period of time but do not provide an initial surge of rapidly released drug that mimics the effect of cigarette inhalation; nasal sprays and inhalers are also available which deal with this problem, but these methods do not permit long term release.

According to the present invention there is provided a method of delivering a substance to the buccal mucosa of a subject, the method comprising providing a tablet comprising a quantity of the substance to be delivered, the tablet having multi-phasic release

properties to release controlled amounts of the substance to the subject over time, and releasing the substance from the tablet in the subject's mouth. The invention also provides a tablet for delivery of a substance to the buccal mucosa of a subject, the tablet comprising a quantity of substance to be delivered to the subject, the tablet having multi-phasic release properties adapted to release controlled amounts of the substance to the subject over time.

The tablet can be of conventional physical design but any vehicle capable of bearing the substance and dissolving in the mouth can be used.

The tablet may have a multi-layer structure with different amounts of substance associated with each layer. This can be by making different homogeneous layers with different release characteristics or by enclosing different quantities of substance within layers of e.g. coating that can dissolve at different rates, thereby deferring the time until the fluids in the mouth dissolve the substance and/or the tablet matrix.

The tablet may comprise a bioadhesive such as Carbopol(TM) or chitosan, or a similar bioadhesive polymer, and this can optionally be in a separate adhesive layer, or can be incorporated into another part of the tablet, such as the slow (or controlled) release layer. The inventors have found that these

compounds also assist in controlling the release of the substance. The tablet may also contain other agents to control the release of the substance such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, poly D L lactide- and/or glycolide-related polymers. Such polymers are very useful in the present invention as they swell when hydrating and this can be used to control the release characteristics of the substance which is retarded in the swollen polymer until the polymer starts to dissociate from the tablet. This can be used to change the release characteristics of the tablet without necessarily changing the amount of substance in the tablet, and without layering the tablet. Thus multi-phasic release properties can be achieved with a homogeneous tablet.

The outer layer of the tablet may be adapted to release a quantity of the substance very quickly to satisfy a craving in the subject for addictive substances.

Typically the substance is nicotine. Other substances are also suitable such as cannabinoids, antibiotics, analgesics or anaesthetics such as lidocaine for direct application to mouth ulcers etc or for use prior to or following dental treatment, and drugs for other buccal infections. In principle, any drug that is suitable for oral administration can be used in the present invention.

Excipients that assist in the penetration of the substance through the buccal membrane can be included, such as bile salts.

The inner layer or layers may be associated with slower release of substance. The layers may contain the substance as an integral component of the layers or the substance may be provided in a separate layer beneath coatings that exhibit the desired release characteristics. For example, the layers may be made up of a material that is adapted to dissolve at a known rate so as to release the substance underneath the layer or trapped within it at a set time after the tablet is placed in the mouth.

Preferably different layers have different release characteristics. For example the outer layers are preferably capable of releasing substance at a different (preferably faster) rate than the inner layers.

In a preferred embodiment the tablet formulation consists of two distinct layers, each of which has a specific function. A controlled release layer containing a bioadhesive is attached to the mucosal tissue lining the cheek adjacent to the gum (gingiva) in the buccal area of the patient's mouth. Upon contact with saliva the rapid release layer disintegrates and releases nicotine, which is subsequently absorbed through the oral mucosa into the systemic circulation. This immediate release and

absorption of nicotine is designed to reduce or eliminate the cravings for nicotine of the smoker, particularly those following a meal (post-prandial cravings). The time period over which the tablet remains attached to the buccal mucosa typically determines the time period over which nicotine is released. This is potentially up to three or four hours. During this period nicotine is being absorbed into the systemic circulation at a constant rate (referred to as zero order release), independent of the amount of nicotine remaining in the formulation, thus eliminating further cravings for nicotine. The user may, at any time, detach and remove the tablet if they think this appropriate. One possible scenario of usage is removal of the tablet prior to eating a meal followed by attachment of a new tablet following completion of the meal.

Various doses of nicotine or other substance can be incorporated into the tablet, in both the rapid and controlled release layers, thus allowing flexibility in reducing regimes for patients and tailoring the formulation to individual patterns of craving for nicotine. The incorporation of different doses of drug does not alter the release mechanism; i.e. it remains rapid from the first layer and zero order from the controlled release layer.

Typical dimensions of the tablet are 6mm diameter and 3mm thickness. These dimensions are usefully independent of nicotine or other substance content as

any reductions in the same are compensated for by increased amounts of diluent to maintain tablet weight and dimension.

For mucoadhesion, Carbopol C934 has been extensively studied and been shown to produce excellent adhesion to mucosal membranes. The bioadhesive strength of this poly (acrylic) acid polymer increases with polymer concentration up to 25% w / w and thereafter remains relatively constant and a tablet containing 5-50 % C934 can adhere to the gingiva for 550-600 minutes. C934 was therefore favoured as the mucoadhesive polymer in the formulation at a preferred concentration of around 20 % w / w where mucoadhesive strength is near maximum and below the 50 % concentration, which has the potential to cause some mucosal irritation.

For controlled drug release from buccal adhesive tablets, HPC is effective in producing controlled drug release.

The layers of the tablet need not be concentric although in certain embodiments this is preferred. In certain embodiments shown in the examples following the tablet has two (or more) flat layers in a "sandwich" structure.

Examples of the invention will now be described by way of illustration, and without limiting the scope

of the invention, with reference to the accompanying drawings, in which:

Fig. 1 is a schematic view of a tablet;

Fig. 2 is a graph of representative nicotine release profiles from dosage forms;

Fig. 3 is a diagrammatric representation of drug release from a poylmer matrix;

Fig. 4 is a graph of release of nicotine from a bi-layer tablet;

Fig. 5 is a schematic diagram of diffusion apparatus used in the methods described;

Fig. 6 is a graph of water uptake profiles for buccal adhesive tablets;

Fig. 7 is a graph of NHT dissolution profiles for buccal adhesive formulations;

Fig. 8 is a graph of diffusional exponent values for nicotine buccal adhesive tablets;

Fig. 9 is a graph of NHT kinetic rate constant values for nicotine buccal adhesive tablets;

Fig. 10 is a graph demonstrating the linear relationship between NHT release rates and HPC content of nicotine buccal adhesive tablets using diffusion dissolution apparatus;

Figs. 11 and 12 are graphs showing dissolution profiles for bilayer tablets; and

Fig. 13 shows drug release profiles of NHT bilayer tablets over the first hour of a 4 hour flow through dissolution test.

Example 1.

Controlled release formulations A - F were produced as shown in Table 1.1, containing nicotine in the form of NHT, PVP to act as a binding agent, lactose as a diluent and magnesium stearate as a lubricant. C934 was included to impart adhesive properties and HPC was included in a range of concentrations to investigate its effect on NHT release. PVP (molecular weight 44000) is included as a binding agent, but also has release-controlling properties. Carbopol(TM) 934P is a synthetic high molecular weight cross-linked polymer, which imparts bioadhesive properties on the formulation. In addition this polymer also has release-controlling and binding properties.

Spray-dried lactose is included as an inert diluent. The physical and chemical properties of this material are ideal for use as such an agent.

HPC is a semi-synthetic polymeric cellulose derivative which has matrix-forming properties. Once hydrated the drug can diffuse out of the matrix. This material thus has drug release controlling properties.

Magnesium stearate was optionally added as a glidant and anti-adherent agent which facilitates powder flow (essential for successful tablet production) and prevents adherence of the powder materials to the tooling of the tablet manufacturing apparatus.

Table 1.1. Excipient concentrations used in the preparation of formulations A - F.

	Excipient composition of tablet mg / tab					
	A	B	C	D	E	F
NHT	10	10	10	10	10	10
PVP (44,000)	6	6	6	6	6	6
C934	20	20	20	20	20	20
HPC	-	10	20	30	40	50
SDL	63	53	43	33	23	13
MGS	1	1	1	1	1	1

NHT = nicotine hydrogen tartrate, PVP = polyvinylpyrolidone, C934 = carbopol, HPC = hydroxypropylcellulose, SDL = spray dried lactose

The excipients were weighed accurately and physically mixed by shaking in a bag for 10 minutes. Powder mixes were used to produce 100 mg tablets by direct compression using an eccentric tablet press (model F3, Manesty machines Ltd, Liverpool, UK) using 6 mm punches.

The dose of nicotine may be varied depending on requirements and a corresponding reduction in mannitol amount maintains tablet dimensions constant. The RRL is optionally formed by mixing the above ingredients and compressing them in a mould of desired shape to form the layer.

Bilayer nicotine buccal tablets were formulated. Burst release of NHT from a rapid release layer to satisfy a craving for nicotine, followed by prolonged release of nicotine from a controlled release layer to prevent reoccurrence of the nicotine cravings.

Rapid release layers (RRL) were formulated using the excipients listed in table 1.2

Table 1.2. Excipient concentrations used in the preparation of RRL layers for bilayer tablet manufacture.

	Excipient composition of rapid release layer mg / layer	
	2 mg RRL	*5 mg RRL*
NHT	2	5
PVP 10,000	4	4
Mannitol	44	41

The excipients were again physically mixed in a bag for 10 minutes. Bilayer tablets were produced using a 2-stage compression cycle. The controlled release layer (CRL) was first formed by direct compression of powder mixes A - F in table 1.1. The CRL was left in the tablet die and the bottom punch lowered. 50 mg of the RRL was added to the die and the second compression carried out. The bilayer tablets were 6 mm x 4.5 mm in dimension and are depicted in figure 1. Bilayer tablets containing both 2 mg and 5 mg RRL were prepared with each CRL (A - F).

The RRL could be distinguished from the CRL layer by the pure white colour of the RRL through the use of mannitol. In a marketed product, the addition of a pharmaceutical pigment would allow the user to distinguish the layers and identify which layer should be attached to the gingiva (gum).

Example 2.

In this example the RRL was as described in example 1 above, and the CRL was as follows:

Table 2

	Amount per tablet / mg (percentage composition)	
Ingredient	CRL 2	
Nicotine	10	(10%)
Magnesium stearate	1	(1%)
PVP*	10	(10%)
Carbopol (TM) 934P	20	(20%)
Spray-dried lactose	19	(19%)
HPC**	40	(40%)

PVP = polyvinyl pyrrolidone, molecular weight 44000.

** HPC = hydroxypropyl cellulose.In each example, the two layers of the overall tablet were separately fabricated; although combined fabrication of whole tablets is generally within the scope of a skilled man. In the present examples the RRL ingredients were mixed and granulated using ethanol as the granulating fluid, followed by compression into tablets; for the CRL the ingredients were dry mixed and tablets formed by direct compression. The two individual tablet layers were then replaced in the die of a tablet press and compressed for a second time, resulting in the formation of one coherent bilayer tablet.

The tablet manufacturing apparatus employed for the fabrication was a standard single punch eccentric press with no modifications. For the rapid production

of larger batches of product a specialised double compression tablet press can be used.

Results for examples 1 and 2.

Using standard BP disintegration apparatus it was found that the rapid release layer completely disintegrated within four minutes. This time is considered acceptable to facilitate rapid absorption of nicotine from the oral mucosa thus eliminating the initial craving of the smoker for nicotine.

The nicotine release from the formulations produced was studied over a four-hour period using standard USP paddle dissolution apparatus and a typical release profile of the results obtained is depicted in Figure 2.

The drug release profiles demonstrate the biphasic nature of the release from the bilayer formulations: an initial burst release of nicotine followed by retarded zero order drug release. This characteristic is absent from the single layer controlled release tablets, which release drug in a monophasic zero order kinetic manner. The initial burst nicotine release is essentially complete within 30 minutes. This result contradicts the disintegration time of the RRL of 4 minutes. However, differences in the hydrodynamic properties of the two test methodologies account for such contradictory results; nonetheless, it is believed that the faster release initially

would sufficiently satisfy initial craving rapidly, and encourage buccal absorption, rather than the swallowing of saliva and consequent unpleasant gastro-intestinal effects.

The mechanism by which drug release is retarded in the controlled release formulations is thought to be due to the formation of a matrix of drug and polymer(s) during fabrication and subsequent contact with the dissolution medium. The drug is evenly dispersed within this matrix, as shown in Fig 3. The dissolution medium can enter through pores in the matrix, dissolve the drug and the resulting drug solution diffuses out of the matrix.

This type of mechanism normally results in first order drug release, as diffusion is a first order process, i.e. the rate of diffusion is dependent on the amount of drug remaining in the formulation. The observation of zero order drug release from the formulations produced is thought to be due to a complex combination of drug diffusion, matrix erosion and interaction of oppositely charged nicotine (cationic) with anionic substituent groups on the Carbopol(TM) molecule, i.e. the -COOH groups.

Example 3

Table 3.1 below shows the formulation ingredient quantities of the controlled release layer of further embodiments A-I. The rapid release layer contained 2

mg NIC, 4 mg PVP 10000 and 44 mg mannitol. The two layers were produced individually by direct compression (8mm punch). Bilayer tablets were produced by manually compressing the two layers together (Manesty F3, Liverpool, UK).

Table 3.1

	Sustained release layers produced. Mass of ingredient per tablet / mg Tablet Formulation Number								
	A	B	C	D	D	F	G	H	I
Ingredient									
NIC	10	10	10	10	10	10	10	10	10
Carbopol	20	20	20	20	20	20	-	-	-
934 (r)	2	4	6	2	4	6	2	4	6
PVP 44000									
HPC	-	-	-	40	40	40	40	40	40
MgS	1	1	1	1	1	1	1	1	1
LactoseTO	100	100	100	100	100	100	100	100	100

PVP = polyvinylpyrrolidone, HPC = hydroxpropylcellulose*
MgS = magnesium stearate

* HPMC can also be used

In vitro drug release was assessed using a dissolution cell method in which the tablet was attached to an artificial dialysis membrane, used to simulate the buccal mucosa, and the drug was released through this into a reservoir of distilled water, and determined by UV spectrophotometry. Other methods used included USP paddle dissolution methods. Zero order release profiles were achieved for batches A-I

over 4 hours. The following table 3.2 demonstrates batches G-I had the highest release rates due to the absence of Carbopol 934P(r). Release rates were decreased in all batches by increasing concentrations of PVP which resulted in decreased layer swelling.

Table 3.2

Zero order release rates of nicotine (diffusion cell)

Formulation	A	B	C	D	E
Dissolution Rate / % min-1	0.26	0.17	0.15	0.25	0.15
Formulation	F	G	H	I	
Dissolution Rate / % min-1	0.12	0.37	0.35	0.37	

Equation 1, an exponential expression used to analyse controlled release behaviour of pharmaceutical systems, was employed to investigate the dissolution data (Peppas and Sahlin, 1989 Int. J. Pharmaceutics 57:169-172).

$M_t / M_\infty = kt^n$ - Equation 1

In this equation, M_t / M_∞ is the fraction of drug released, k is the kinetic constant and n is the diffusion exponent for drug release. This equation can be applied to the first 60 % of drug release to identify the type of drug release from the system. A plot of log (M_t / M_∞) versus log t gives a straight line of gradient n and intercept log k.

Diffusion cell results (n = 0.69-0.93) indicated the overall drug release mechanism was non-Fickian controlled by a combination of NIC diffusion and polymer chain relaxation r^2 = 0.88-0.97).

Fig. 4 shows release profiles from tablets (US paddle) and demonstrates the efficient release from the rapid release layer of sample I (98% of the nicotine was released after 10 minutes).

Example 4

Dosage forms formulated as above were tested to ensure that the patient receives a product containing the required amount of drug substance in a form that enables the drug substance to exert its full pharmacological action. The standard tests included uniformity of weight, uniformity of content, disintegration (where appropriate) and dissolution, and the non-standard crushing strength and resistance to abrasion tests.

Ten tablets from each tablet batch were selected and weighed accurately to 4 decimal places using an analytical balance (model AE 50, Mettler instruments LTD, High Wycombe, U.K.). The tablet weights were averaged and a relative standard deviation value calculated.

Three tablets from each batch were weighed and the theoretical NHT content was calculated. Each tablet

was then powdered and placed in a standard flask and allowed to dissolve in 50 mL of HPLC mobile phase. To facilitate the solution of the water swellable polymers within the tablet matrix, and ensure complete NHT release from the polymers, the flasks were placed in an ultrasonic bath for 60 minutes, left overnight and then placed in the sonic bath for a further 60 minutes. The solutions were filtered under gravity using filter paper, diluted appropriately and the NHT content assayed using an analytical HPLC method.

The crushing strength test involves application of a compressive load to the tablet to induce breaking. Sophisticated testers apply the force at a constant rate to improve reproducibility over simple hand operated devices. However, even when the load is applied at a constant rate, the variation in strength within a batch may be considerable.

Five tablets from each batch were placed in a tablet hardness tester (model TBH 28, Erweka, Heusenstamm, Germany). The values were averaged and a relative standard deviation value was calculated.

It is likely that a tablet, during a normal life, will be exposed to forces in production, packaging or transportation procedures. These forces whilst not severe enough to break the tablet, may abrade small particles from its surface. To assess the resistance to abrasion, a friability tester is used, which

subjects tablets to a uniform tumbling action, for a specified time, and the weight loss from the tablets is measured.

Five tablets from each batch were weighed collectively and the weight noted. The tablets were then placed in a friability tester (model TA, Erweka, Heusenstamm, Germany). After 5 minutes, the five tablets were re-weighed and the percentage weight loss was calculated.

A swellable matrix is used to control the release of drug, and polymer swelling is an important stage in the formation of a mucoadhesive bond between such formulations and the mucosa. *In vitro* swelling studies were therefore carried out.

Three tablets from each batch were placed on a plastic mesh (1 cm^2) to allow handling of the tablet without direct touching. The tablet / mesh assembly was weighed accurately to 4 decimal places and the weight noted. The axial and radial dimensions of the tablets were measured using sliding scale callipers. Each tablet assembly was placed in separate glass vials containing 4 ml of deionised water. At specific time intervals over 24 hours, the tablet assembly was removed from the vials and any surface moisture was carefully removed using filter paper. The assembly was re-weighed and the axial and radial dimensions were again noted. The percentage increase

in weight, axial and radial dimensions was calculated.

In Vitro NHT dissolution was analysed using two different methods. The first involved flow through dissolution apparatus, where the buccal adhesive tablets were exposed to 20 mL dissolution medium. The second method is a novel method, devised to more accurately represent the *in vivo* conditions to which a buccal adhesive tablet might be exposed. The method used a transdermal tester and following NHT dissolution from the tablet in a small volume (< 0.5 mL) the detected NHT diffuses across a membrane in to a 5 mL cell.

Three tablets from each batch were weighed and the theoretical nicotine contents were calculated and noted. The tablets were placed separately in a 20 mL cell in the flow through dissolution tester. The dissolution medium was distilled water supplied at a flow rate of 100 $mLhr^{-1}$ by a pump (model 202u, Watson - Marlow, Falmouth, U.K.) and at 37°C from an electric water heater (model W14, Grant Instruments, Cambridge, U.K.). The effluent from the cells was collected over a 4 hour period and assayed at certain time intervals using U.V. detection at 259 nm (model UV 300, Unicam LTD, Cambridge, U.K.).

A transdermal tester as shown in Fig. 5 (model HDT 10, Copley Scientific Ltd., Nottingham, U.K.) was

used for testing diffusion of the substance across a cell membrane.

Tablets from each batch were weighed and the theoretical nicotine contents were calculated and noted. The experimental membrane was secured tightly to the cells, as show above. Single layer visking dialysis membrane or porcine buccal mucosa was used as the test membrane. Buccal mucosa was collected and prepared. Porcine mucosa was used the same day as the animal was sacrificed. The 5 mL cells were then filled with distilled water from the solution reservoir and the clamps secured. The cell stirrers and the cell heater were switched on to heat the solution to 37°C. To start, 100 µL of water was placed on the upper side of the membrane and the tablet was placed gently on the surface. 50 µL of water was added to the tablet and membrane interface at 30 minute intervals using an automatic pipette to maintain adequate wetting of both the tablet and the membrane. At certain time intervals, 5 mL samples were withdrawn from the cells and the nicotine content and hence the percentage nicotine released from the tablet was investigated over a 4 hour period using U.V. analysis. The dissolution runs were repeated in triplicate for each batch. The area available for drug permeation in to solution was 0.785 cm^2.

The results of the uniformity of weight experiment are tabulated in table 4.1.

Table 4.1. Uniformity of weight for batches A - F (n=10).

Tablet	A	B	C	D	E	F
Mean Weight / mg	100.69	100.10	100.31	100.32	99.90	100.29
(RSD / %)	(0.732)	(0.309)	(0.268)	(0.387)	(0.293)	(0.394)

The expected weight of the tablets was 100 mg. All tablet weights were 100 mg ± 2 mg. The average weight from 10 tablets in each batch was 100 mg ± 1 mg. Additionally the variation in tablet weights within each batch was very low as indicated by the low percentage relative standard deviation values in table 4.1. It can therefore be concluded that the dry mixing and direct compression of the tablets produces a uniform batch with regard to tablet weight.

The NHT recovered during the assay is quoted as a percentage of the theoretical NHT in the tablet (10 % of tablet weight). The mean percentage NHT recovered for each tablet batch is tabulated below in table 4.2.

Table 4.2. Uniformity of active ingredient for batches A - F (n=3).

Tablet	A	B	C	D	E	F
Mean NHT recovered / % (RSD / %)	98.74 (3.95)	98.60 (1.88)	100.15 (3.23)	97.66 (2.46)	96.70 (1.23)	95.78 (0.78)

The assay results showed that not one tablet contained greater or less than 5 % of the theoretical nicotine content of the tablet. Combined with the

low deviation of tablet weights means that the tablets contained 10 mg ± 0.5mg NHT. These results fall well within the limits of 90 - 110% set out by the British Pharmacopoeia. The low standard deviations achieved again confirm that the method of tablet manufacture is suitable for producing uniform tablet batches.

The mean tablet crushing strengths are shown below in table 4.3.

Table 4.3. Tablet crushing strength for batches A - F (n=5).

Formulation	A	B	C	D	E	F
Mean crushing strength / Newtons (RSD / %)	156.0 (5.82)	140.8 (10.52)	142.6 (8.31)	154.4 (4.16)	174.6 (3.05)	183.6 (0.98)

Few conclusions may be drawn from the data in table 4.3. Formulations A - D do not show marked differences in crushing strength and combined with the relatively large standard deviations firm conclusions may not be drawn. Formulations E and F with 40 % and 50 % HPC show slightly higher crushing strengths than the other formulations, perhaps due to the ability of HPC to act as a binding agent. There are no recommendations for buccal release tablets and as the tablets are designed to swell as opposed to disintegrate and dissolve as with an oral tablet, the higher values noted are perhaps appropriate.

The percentage weight loss of five tablets from each batch after 5 minutes friability testing is tabulated in table 4.4.

Table 4.4. Tablet friability results; Weight loss from batches A - F.

Tablet	A	B	C	D	E	F
Weight loss / %	0.12	0.06	0.06	0.02	0.08	0

As discussed earlier, the friability tests are designed to simulate conditions that may be experienced by a tablet during production, packaging and transportation. The weight loss from the tablets has been demonstrated to be extremely low perhaps as a function of the tablet hardness. These results indicate that such a formulation would be resistant to abrasion and therefore resistant to loss of tablet weight including the loss of active ingredient through normal processes until the product is used.

The water uptake profiles of formulations A- F are shown in figure 6.

As can be clearly seen from figure 6, the swelling profile formulation A is considerably greater than observed for formulations B - F. Over the first 6 hours, formulation A has a more rapid weight increase due to a greater uptake of water. The formulation then continues to take up water over the 24 hour test period resulting in a 175.5 % (± 2.55 % RSD) weight increase compared with the dry tablet weight. This

larger and more rapid weight increase is due to the absence of HPC from the formulation, which allows the hydrophilic polymer carbopol to uptake the water in to the buccal tablet. Figure 6 also indicates that there is little or no difference between the swelling profiles of formulations B - F, which contain between 10 and 50 % HPC. These formulations do not swell to a great extent after the first 6 hours. Formulation B gains an average of 13.5 % in weight between 6 and 24 hours, formulations C - F gain between 1.39 and 4.27 %, which suggests that the formulations are approaching maximal swelling at approximately 6 hours. The addition of HPC to the formulation appears to counteract the strong swelling properties of carbopol, this may be explained by the hydrated matrix properties of HPC which controls the penetration of water into the tablet. Concentrations of 20 - 50 % HPC show no significant difference in weight gain (swelling rate) between 6 - 24 hours.

The tablet dimensions measured over the 24 hour period showed similar trends compared to the weight increase. Despite large experimental standard deviations (2.5 - 33 % RSD), due to the difficulty of measuring a soft hydrated tablet, an increase in the HPC concentration of the formulation resulted in a smaller size increase of the tablet. The dimensions of formulation A increased to a larger extent than formulations B - F, which swelled to a comparable extent. This may again be explained by the matrix forming properties of HPC, which controls the uptake

of water by the formulation. The tablet size increase for formulations B - F between 6 and 24 hours is again very small, again suggesting that at 6 hours the tablets are approaching maximal swelling. The actual data is recorded in tables 4.5. and 4.6.

Table 4.5. Axial swelling of buccal bioadhesive tablets

	Axial size increase / %					
Time / Hours	*A*	*B*	*C*	*D*	*E*	*F*
0.5	11.92	14.70	9.36	12.16	14.76	5.28
1	17.02	20.57	13.10	23.83	26.19	9.72
2	28.84	28.43	29.00	32.71	34.76	10.28
3	33.99	30.39	29.95	35.03	34.29	14.45
4	38.54	30.88	36.45	36.91	35.72	17.39
6	47.13	32.84	38.35	37.38	40.48	20.82
24	60.23	43.14	35.08	37.38	37.14	27.20

Table 4.6. Radial swelling of buccal bioadhesive tablets

	Radial size increase / %					
Time / Hours	*A*	*B*	*C*	*D*	*E*	*F*
0.5	14.17	11.11	14.44	11.39	13.89	6.32
1	15.56	13.33	15.00	15.00	15.28	13.56
2	23.33	19.45	18.89	22.67	17.50	19.37
3	28.89	20.56	22.22	21.39	17.50	20.34
4	32.50	25.56	27.78	26.39	17.22	28.05
6	37.78	26.11	32.22	27.78	22.78	27.60
24	60.00	35.28	32.78	30.83	28.61	27.62

One theoretical model of mucoadhesion suggests that 3 stages are involved, namely; intimate contact, interpenetration of mucus / polymer macromolecules and formation of secondary non-covalent bonds. Intimate contact between the mucoadhesive and the

mucus requires the swelling and spreading of the bioadhesive material to result in a close or intimate contact. The axial tablet dimension, which would be in contact with the mucosal membrane, swells on average by 11.3 % in 30 minutes and should be sufficient to produce the intimate contact required for mucoadhesion.

The swelling study may also be of importance when assessing the dissolution behaviour of these formulations. HPC, a semi-synthetic polymeric derivative of cellulose, will swell in an aqueous medium to form a gel-like matrix that controls release by acting as a barrier to drug dissolution and diffusion. The HPC gel acts as a physical barrier through which the dissolution medium must penetrate to dissolve the drug, the drug solution must then again penetrate the gel to be available for absorption. Carbopol on the other hand is hydrophilic and will swell faster and to a greater extent, promoting the penetration of the dissolution medium into the tablet matrix. The alteration of polymer content of the matrix will alter the drug release rate. Formulation A containing no HPC should allow the dissolution medium to penetrate the tablet, dissolve the drug and diffuse out of the tablet, resulting in rapid drug release. Formulations B - F containing increasing HPC content should retard drug release by forming the gel barrier resulting in controlled drug release over a number of hours. Due to the small differences in swelling of formulations

B - F, it is not possible to predict any differences with regard to drug dissolution.

Nicotine release profiles for formulations A - F are shown in figure 7.
From figure 7 it can be seen that only approximately 50 - 60 % drug release was achieved form the formulations. HPC was expected to control the release in such a manner over the 4 hour period, it is therefore surprising that formulation A containing no HPC released only 60 % of NHT in this time.

The dissolution data was investigated using equation 1 as defined above (Peppas and Sahlin, 1989). The data from these plots are presented in table 4.8.

The calculated n value allows the release mechanism from a cylindrical system such as a tablet to be characterised according to table 4.7. (Peppas and Sahlin 1989).

Table 4.7. Diffusion exponent and solute release mechanism

Diffusion exponent (n) from a cylinder	*Release mechanism*
0.45	Fickian Diffusion
0.45 < n < 0.89	Anomalous transport
0.89	Case II transport

Fickian diffusion describes t^{-2} kinetics and case II transport describes constant zero order drug release. Polymer swelling and drug diffusion through a matrix

do not normally follow Fickian release behaviour, due to the existence of a molecular relaxation process (Vigoreaux and Ghaly 1994 Drug Development and Industrial Pharmacy 20(16) 2519-2526). This type of drug release results in intermediate values for n and is classed as anomalous (non Fickian) transport.

Table 4.8. Diffusional exponents (n) and kinetic constants (k) for NHT dissolution from buccal adhesive nicotine tablets (n=3).

Formulation	*Diffusional exponent (n) (RSD / %)*	*Kinetic constant / hr^{-1} (k) (RSD / %)*	*r^2 (RSD / %)*	*Release mechanism*
A	0.6857 (12.05)	0.2520 (14.07)	0.974 (0.27)	Anomalous transport
B	0.7200 (6.75)	0.2174 (7.20)	0.987 (0.59)	Anomalous transport
C	0.8413 (2.83)	0.1940 (4.19)	0.982 (0.84)	Anomalous transport
D	0.8341 (5.31)	0.1855 (0.22)	0.994 (0.73)	Anomalous transport
E	0.7778 (9.26)	0.1905 (3.85)	0.976 (1.40)	Anomalous transport
F	0.7768 (9.78)	0.1915 (8.71)	0.983 (0.357)	Anomalous transport

The n value for formulation A is almost exactly mid range for anomalous non-Fickian release mechanism. However, the n value increases in the other formulations that contain HPC. Formulations C and D containing 20 and 30 % HPC respectively show n values approaching case II transport i.e. zero order NHT release. For formulations E and F containing 40 and

50 % HPC, the n values appear to tail off. This suggests the most appropriate matrix for NHT release contains around 20 - 30 % HPC providing release approaching zero order. The variation of the diffusional exponent (n) with HPC is summarised in figure 8.

The kinetic rate constants (k) in table 4.8 incorporate the structural and geometrical characteristics of the release device and may be used to compare formulations. Formulation A, containing no HPC exhibits the greatest rate constant (k). The addition of HPC, as a matrix former results in a decrease in the rate constant as the hydrated HPC provides a barrier to drug dissolution. The rate decreases to a minimum at 30 % and remains relatively constant with increasing HPC concentration. The variation in kinetic rate constant with HPC content is shown graphically in figure 9.

NHT dissolution using the diffusion dissolution method followed zero order release kinetics using the dialysis visking tubing as the model membrane. The dissolution statistics are presented in table 4.9.

Table 4.9. NHT release rates from nicotine buccal adhesive tablets (n=3)

Formulation	*Release rate / %hr^{-1}*	*(RSD / %)*	*r^2*	*(RSD / %)*
A	4.4969	(2.41)	0.989	(0.58)
B	3.9375	(3.42)	0.938	(4.23)
C	3.4169	(2.66)	0.983	(0.53)
D	2.7309	(9.54)	0.983	(0.52)
E	2.8778	(7.91)	0.984	(1.45)
F	2.6863	(16.02)	0.994	(0.34)

Zero order case II transport was confirmed by analysis of the dissolution data using equation 1 as described above. Diffusion exponent (n) values were between 0.89 and 1.45 in all formulations except formulation B (n = 0.75). The lower correlation value and larger RSD value for formulation B in table 4.9. may explain this.

The release rates quoted in table 4.9. again appear to decrease with increasing HPC concentration. This decrease in release rate appears to be linear to a concentration of 30 % as can be seen in figure 10.

HPC contents of 30 % and above (formulations D, E and F) produce NHT release rates that are not significantly different ($p > 0.05$). This agrees with the trend shown by the NHT release for the flow through dissolution method and suggests that HPC concentrations of above 30 % are not necessary to produce a sustained release matrix for NHT.
It is worth noting that the release rates across the dialysis visking tubing for formulation A are not significantly different from the permeation rates of

nicotine from solution through the same membrane seen in section 3.3.4.1. This suggests that limiting factor to drug dissolution using this method is in fact permeation across the membrane resulting in zero order kinetics. When HPC is present in the formulation, however, these rates decrease further. Over the 4 hours, a maximum of 17 % NHT was released, this decreased to 11.5 % for formulation F. When compared with the results from the flow though dissolution (50 - 60 %) this value is low, but may be due to the nature of the membrane.

The diffusion dissolution apparatus was set up using porcine buccal membrane. Due to the limited supply of porcine mucosa, this experiment was carried out once with formulation A. Using HPLC detection, only 1.4 % of the NHT content of the tablet was recovered in the receptor solution after 4 hours. This figure is very low compared with the artificial membrane and may be due to the thickness of the membrane and problems of using animal tissue. The experiment was repeated using formulation A and fresh porcine mucosa, however instead of sampling from the receptor solution, after 4 hours that tablet was assayed to determine the NHT remaining in the formulation. Following this method, the HPLC tablet assay detected 6.95 mg of NHT remaining, which was calculated to be 69 % of the NHT content of the tablet. It could therefore be concluded that 31 % of the available NHT (3.11 mg) had been released from the tablet. All the NHT release was not able to cross the porcine

membrane and enter the receptor solution, most likely due to the 2 mm thickness of the membrane (the upper 200 μm is known to be the barrier to buccal permeation) and the small orifice (0.785 cm^2) available for the NHT to enter the receptor solution. From this data it is suggested that the NHT has been released from the formulation and partitioned into the buccal tissue; however due to the reasons mentioned above, the NHT remained in the tissue and was not passed into the receptor solution.

All bilayer tablets weighed 150 mg ± 3 mg. The average weights of 3 tablets from all batches ranged from 149.0 mg to 150.5 mg with a corresponding percentage relative standard deviation value of 0.17 % to 1.19 %. These results suggest that the method of preparation is suitable in producing bilayer tablets of uniform weight.

Two formulations were selected in the determination of active ingredient content, formulation CRL B + RRL 2 mg and formulation CRL D + RRL 5 mg. The NHT recovered during the assay is quoted as a percentage of the theoretical NHT in the tablet.

Table 4.10. Uniformity of active content for two bilayer tablet formulations (n=3).

CRL	*RRL*	*Mean NHT recovered / %*	*RSD / %*
A	2	98.52	1.73
D	5	98.88	1.08

All of the tablets assayed contained 100 % ± 2.5 % of the theoretical NHT content. This, combined with the low deviations quoted in table 4.10 again suggests that the method of manufacture of the bilayer tablets is suitable for producing a tablet of uniform active content.

One bilayer tablet formulation was selected to carry out the crushing strength determination using the method outlined for formulations A - F. The mean crushing strength (n=5) for formulation CRL B + RRL 2 mg was 167.4 N (5.08 % RSD). This value is significantly higher ($p < 0.05$) than the formulation B controlled release monolayer alone. This is probably due to the double compression cycle of the bilayer tablet resulting in a harder tablet.

Formulation CRL B + RRL 2 mg was again used for the friability determination using the method outline for formulations A - F. During the 5 minute friability test, 5 tablets lost 0.15 % of their combined weight. This is higher that the 0.06 % for formulation B controlled release monolayers alone, however this value is still low. The two layers remained joined and intact after the 5 minute test. This suggests that the bilayer tablets would be resistant to abrasion and therefore resistant to loss of tablet weight, including the loss of active ingredient, through normal processes until the product is used.

NHT release from the bilayer tablets was analysed using the flow through dissolution method outlined

above. Release profiles for bilayer tablets containing controlled release layers A and E are shown in figures 11 and 12. These profiles are representative of the trends seen in the release behaviour of all bilayer tablets.

Figures 11 and 12 show that the bilayer tablets produce a biphasic drug release profile, with a more rapid release of nicotine over the first hour of dissolution testing. Additionally, the rate of drug release from the bilayer tablet with the 5 mg RRL was greater than that from the bilayer tablet containing the 2 mg RRL. This trend was seen in all bilayer tablet batches produced. The bilayer tablets containing the 2 mg RRL released all the NHT content in, on average 26.25 minutes, ranging from 25 to 30 minutes (n=18). The 5 mg RRL released all the NHT in, on average 43.3 minutes, ranging from 40 - 47.5 minutes (n=18).

After 1 hour, the drug release profiles level out and appear parallel to tablets containing no RRL. This trend was confirmed by analysis of the dissolution data from 1 to 3 hour time period. There was no significant difference ($p > 0.05$, n=3) in the gradients of the lines (release rates) over this time scale for the CRL alone, the CRL and 2 mg RRL and the RRL and 5mg RRL bilayer tablets. This confirmed that after one hour, release rates were governed by the CRL alone with no contribution by the RRL.

To determine the NHT release profile of the RRL over the first hour of dissolution testing, bilayer tablets containing CRL A and CRL B with the 2 mg RRL were subjected to flow through dissolution over one hour with more frequent sampling times. The NHT release profiles are shown in figure 4.10.

Figure 4.10. indicates that the NHT release from bilayer tablets over the first hour followed zero order release kinetics. The time taken for the bilayer tablet to release the 2 mg NHT was 27.78 minutes (8.44 % RSD). This compares favourably to the 26.35 minutes identified above. Due to the agreement in results, the one hour dissolution experiment was not repeated with the 5 mg RRL.

Dissolution data was again analysed using equation 1. The results are presented in table 4.11.

Table 4.11. Diffusional exponents (n) and kinetic constants (k) for NHT dissolution from buccal adhesive nicotine tablets (n=3).

1

CRL	*RRL*	*Diffusional Exponent (n) (RSD / %)*	*Kinetic Constant / hr^{-1} (k) (RSD / %)*	*r^2 (RSD / %)*	*Release Mechanism*
A	-	0.6857	0.2520	0.974	Anomalous
		(12.05)	(14.07)	(0.27)	transport
A	2	0.6383	0.3341	0.965	Anomalous
		(19.10)	(11.55)	(0.79)	transport
A	5	0.5926	0.3717	0.946	Anomalous
		(9.86)	(4.51)	(0.65)	transport
B	-	0.7200	0.2174	0.987	Anomalous
		(6.75)	(7.20)	(0.59)	transport
B	2	0.5882	0.3426	0.962	Anomalous
		(20.71)	(13.74)	(1.14)	transport
B	5	0.4961	0.3896	0.929	Anomalous
		(3.57)	(6.02)	(1.59)	transport
C	-	0.8413	0.1940	0.982	Anomalous
		(2.83)	(4.19)	(0.84)	transport
C	2	0.6020	0.3444	0.970	Anomalous
		(13.94)	(8.33)	(2.06)	transport
C	5	0.4853	0.4154	0.932	Anomalous
		(6.80)	(6.26)	(2.02)	transport
D	-	0.8341	0.1855	0.994	Anomalous
		(5.31)	(0.22)	(0.73)	transport
D	2	0.7075	0.2894	0.956	Anomalous
		(3.23)	(5.52)	(1.05)	transport
D	5	0.4695	0.4128	0.962	Anomalous
		(26.60)	(12.84)	(2.08)	transport
E	-	0.7778	0.1904	0.976	Anomalous
		(9.26)	(3.85)	(1.40)	transport
E	2	0.5639	0.3402	0.988	Anomalous
		(12.77)	(7.35)	(0.91)	transport
E	5	0.5023	0.4066	0.945	Anomalous
		(8.00)	(2.46)	(1.06)	transport
F	-	0.7768	0.1915	0.983	Anomalous
		(9.78)	(8.71)	(0.983)	transport
F	2	0.5892	0.3024	0.938	Anomalous
		(20.00)	(8.57)	(3.27)	transport
F	5	0.4823	0.3588	0.921	Anomalous
		(10.21)	(8.36)	(4.35)	transport

The calculated n values are all within the range indicating anomalous non-Fickian release mechanism. However table 4.11. indicates that the n values for the bilayer tablets containing 5 mg RRL are lower than for the bilayer tablet containing the 2 mg RRL and both are lower that the CRL monolayers alone. The n values for the monolayers, as discussed earlier, approached zero order release. The addition of the 5 mg RRL results in this value decreasing and the mechanism of release, although still anomalous transport, now approaches Fickian type release where drug release occurs by diffusion of the drug due to a chemical potential gradient. The departure from zero order release may be explained by the distinct biphasic release profiles identified above, where rapid release from the RRL occurs over the first hour, followed by NHT release approaching zero order kinetics over the remaining 3 hours.

Modifications and improvements can be incorporated without departing from the scope of the invention. For example in many embodiments the tablet can include a sugar such as mannitol, sucrose or glucose that can contain the substance to be released within the tablet and can also improve the taste of the tablet in the mouth. Any sugar can be suitable for this purpose.

Claims

1. A method of delivering a substance to the buccal mucosa of a subject, the method comprising providing a tablet comprising a quantity of the substance to be delivered, the tablet having multi-phasic release properties to release controlled amounts of the substance to the subject over time, and releasing the substance from the tablet in the subject's mouth.

2. A method as claimed in claim 1, wherein the tablet has a multi-portion structure and different amounts of substance are released from each portion.

3. A method as claimed in claim 1 or claim 2, wherein the tablet has a multi-portion structure and the different portions release substance at different rates.

4. A method as claimed in any preceding claim, wherein the tablet is attached to the buccal mucosa by a bioadhesive.

5. A method as claimed in claim 4, wherein the bioadhesive comprises one or more of carbopol, chitosan, hydroxypropyl cellulose, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose.

6. A method as claimed in claim 4 or claim 5, wherein the bioadhesive is disposed in a localised portion of the tablet.

7. A method as claimed in any preceding claim, wherein the tablet contains agents to control the release of the substance.

8. A method as claimed in claim 7, wherein the release-controlling agents comprise one or more of hydroxypropylmethyl cellulose, hydroxypropyl cellulose, poly D L lactide- and glycolide-related polymers.

9. A method as claimed in any preceding claim, wherein a portion of the tablet releases a quantity of the substance quickly to satisfy a craving in the subject for addictive substances.

10. A method as claimed in any preceding claim, wherein the substance comprises one or more of nicotine, cannabinoids, antibiotics, analgesics and anaesthetics.

11. A method as claimed in any preceding claim, wherein the substance is provided in a localised portion having a coating that exhibits the desired release characteristics.

12. A method as claimed in any preceding claim, wherein the tablet is a multi-layer tablet and

the layers have different release characteristics.

13. A method as claimed in claim 12, wherein an outer layer releases substance at a faster rate than an inner layer.

14. A method as claimed in any preceding claim, wherein the tablet formulation comprises a controlled release layer containing a bioadhesive for attachment to the buccal mucosa and release of substance at a constant rate, and a rapid release layer for rapid release of substance into the systemic circulation through the oral mucosa.

15. A method as claimed in any preceding claim, wherein the tablet comprises concentric layers.

16. A method as claimed in any one of claims 1-14, wherein the tablet has two (or more) flat layers in a sandwich structure.

17. A tablet for delivery of a substance to the buccal mucosa of a subject, the tablet comprising a quantity of substance to be delivered to the subject, the tablet having multi-phasic release properties adapted to release controlled amounts of the substance to the subject over time.

18. A tablet according to claim 17, having a multi-portion structure with different rates of release of substance associated with each portion.

19. A tablet according to claim 18, having different homogeneous portions with different release characteristics.

20. A tablet according to claim 18 or claim 19, having different quantities of substance associated with respective portions.

21. A tablet according to any one of claims 18-20, wherein an inner portion is adapted for slower release of substance than an outer portion.

22. A tablet according to any one of claims 18-21, wherein the outer portion of the tablet is adapted to release a quantity of the substance quickly.

23. A tablet according to any one of claims 18-22, wherein the respective portions contain a homogeneous dispersion of the substance throughout each portion.

24. A tablet according to any one of claims 18-23, wherein the substance is provided in a discrete portion having a coating that exhibits the desired release characteristics.

25. A tablet according to any one of claims 17-24 wherein the tablet has a multi-layer structure.

26. A tablet according to claim 25, wherein the layers of the tablet are concentric.

27. A tablet according to claim 25, wherein the tablet has two or more flat layers in a sandwich structure.

28. A tablet according to any one of claims 17-27, comprising a bioadhesive.

29. A tablet according to any one of claims 17-28, having a controlled release layer containing a bioadhesive for attachment to the buccal mucosa and sustained release of the substance at a relatively constant rate, and a rapid release layer for rapid release of the substance upon contact with saliva in the mouth.

30. A tablet according to claim 28 or 29, wherein the bioadhesive is in a localised portion of the tablet.

31. A tablet according to any one of claims 28-30, wherein the bioadhesive comprises one or more of carbopol, chitosan, hydroxypropyl cellulose, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose.

32. A tablet according to any one of claims 17-31, containing agents to control the release of the substance.

33. A tablet according to claim 32, wherein the agent comprises one or more of hydroxypropylmethyl cellulose, hydroxypropyl cellulose, poly D L lactide- and glycolide-related polymers.

34. A tablet according to any one of claims 17-33, wherein the substance is nicotine.

35. A tablet according to any one of claims 17-33, wherein the substance comprises one or more of cannabinoids, antibiotics, analgesics and anaesthetics, and drugs for buccal infections.

36. A homogeneous tablet according to claim 18.

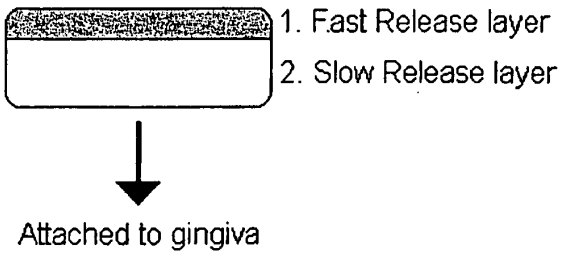
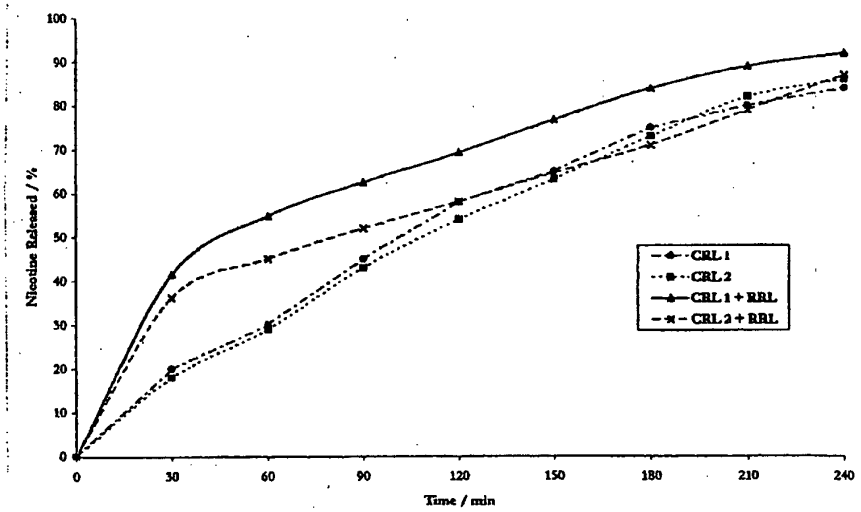

1. Fast Release layer
2. Slow Release layer
Attached to gingiva

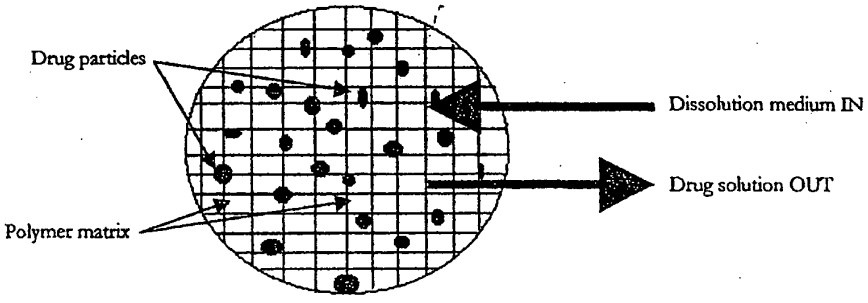
Figure 1.

FIG 2



Representative nicotine release profiles from the buccal bioadhesive formulations produced in this study.

FIG 3



Diagrammatic representation drug release from a polymer matrix.

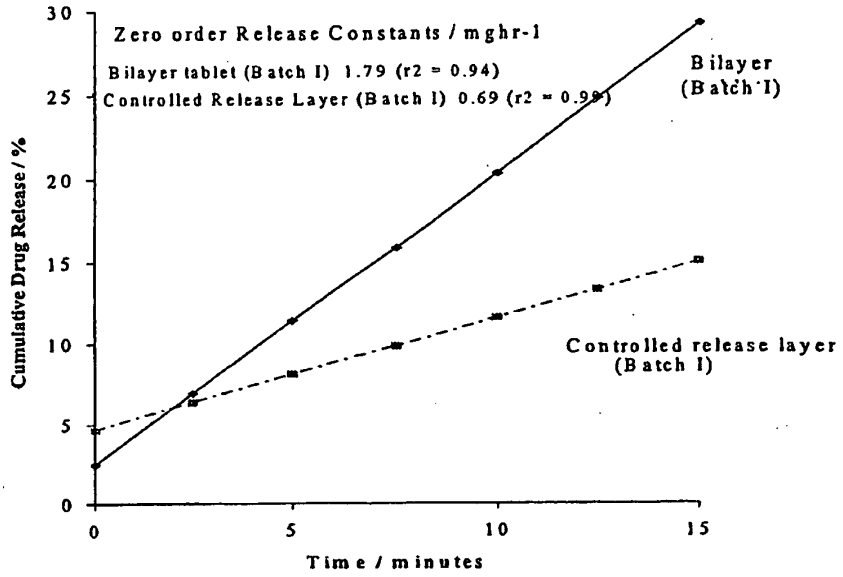

Zero order Release Constants / mghr-1
Bilayer tablet (Batch I) 1.79 (r2 = 0.94)
Controlled Release Layer (Batch I) 0.69 (r2 = 0.98)
Bilayer (Batch I)
Controlled release layer (Batch I)
Cumulative Drug Release / %
Time / minutes
0
5
10
15
20
25
30

fig 1

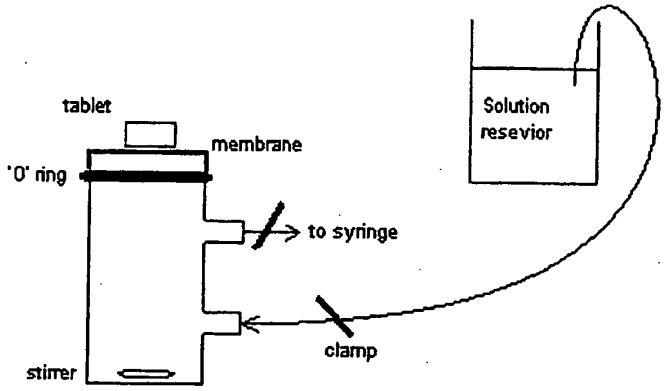


Figure 5. Diffusion dissolution apparatus

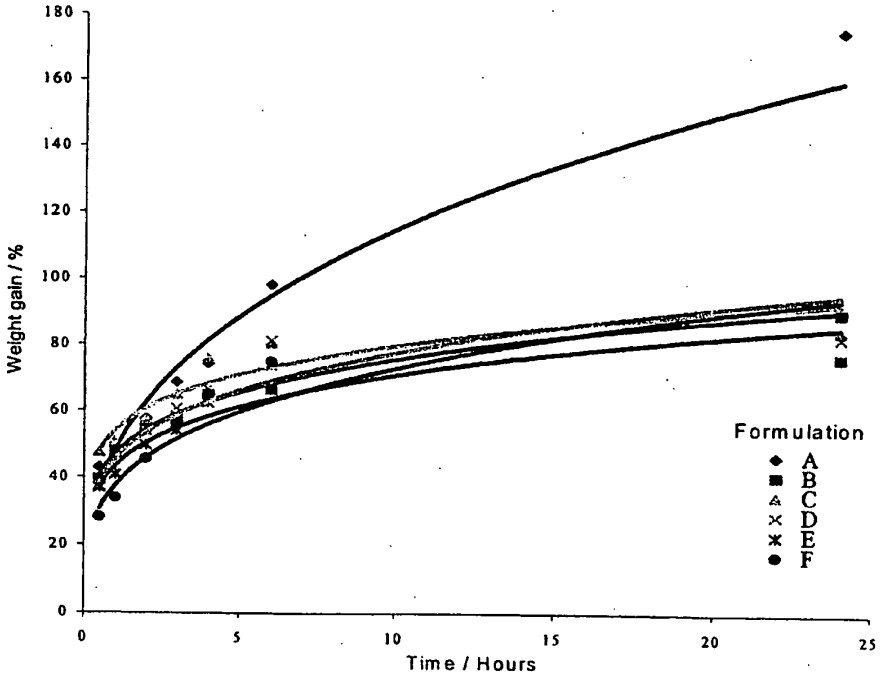


Figure 6. Water uptake profiles for buccal adhesive tablet batches A - F (n=3).

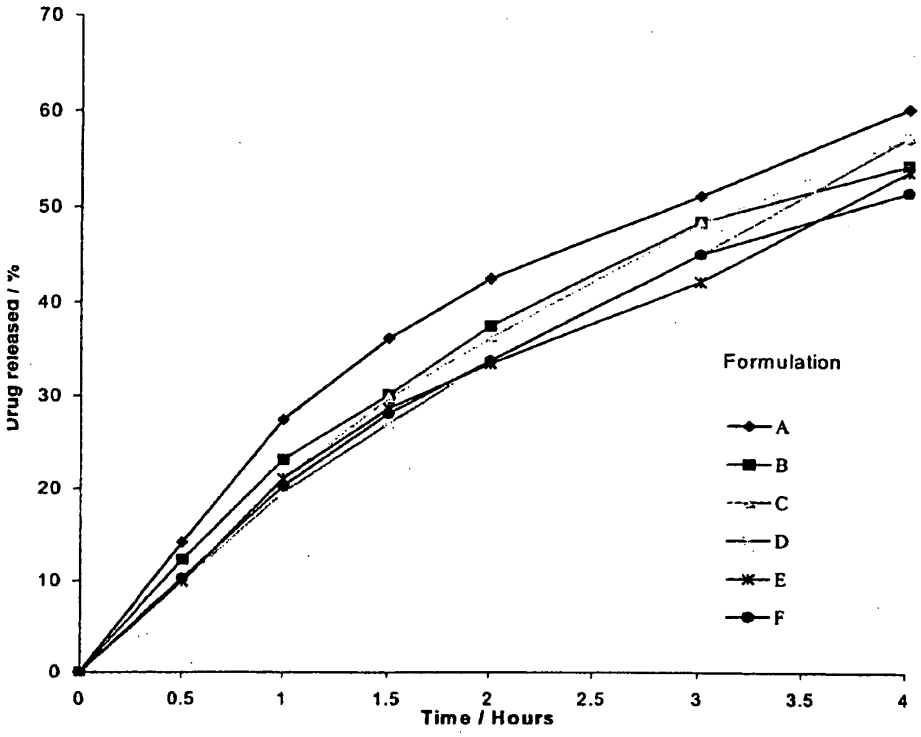


Figure 7. NHT dissolution profiles for buccal adhesive formulations A - F.

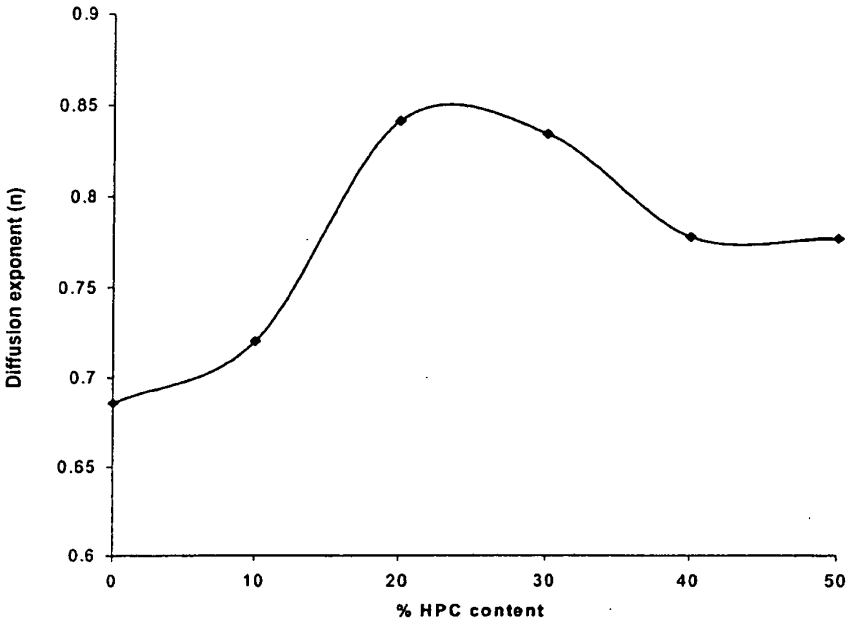


Figure 8. Diffusional exponent (n) values for nicotine buccal adhesive tablets

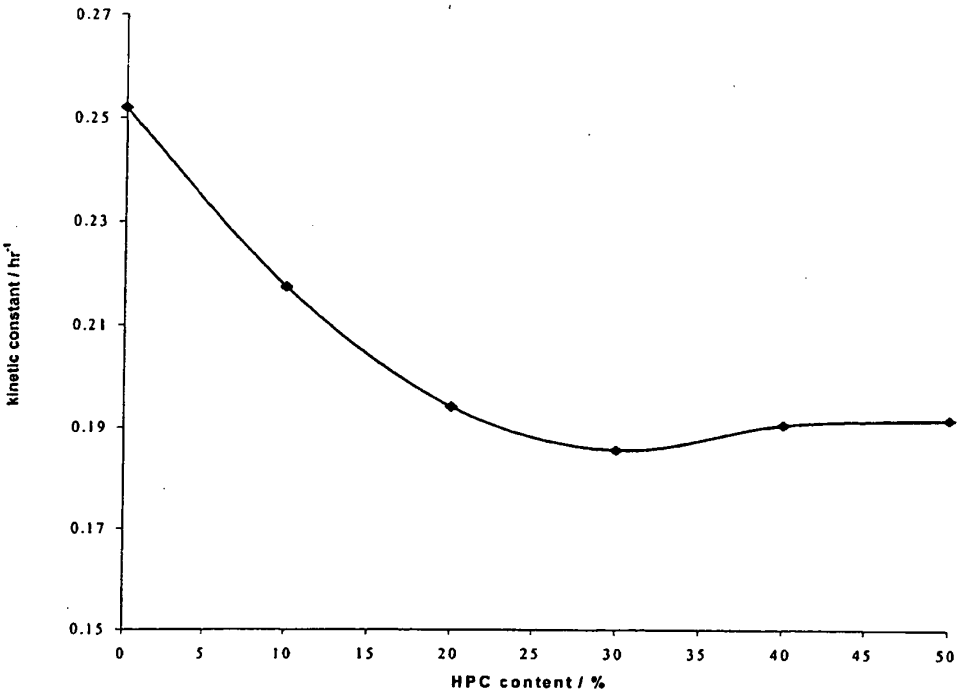


Figure 9. NHT kinetic rate constant values (k) for nicotine buccal adhesive tablets

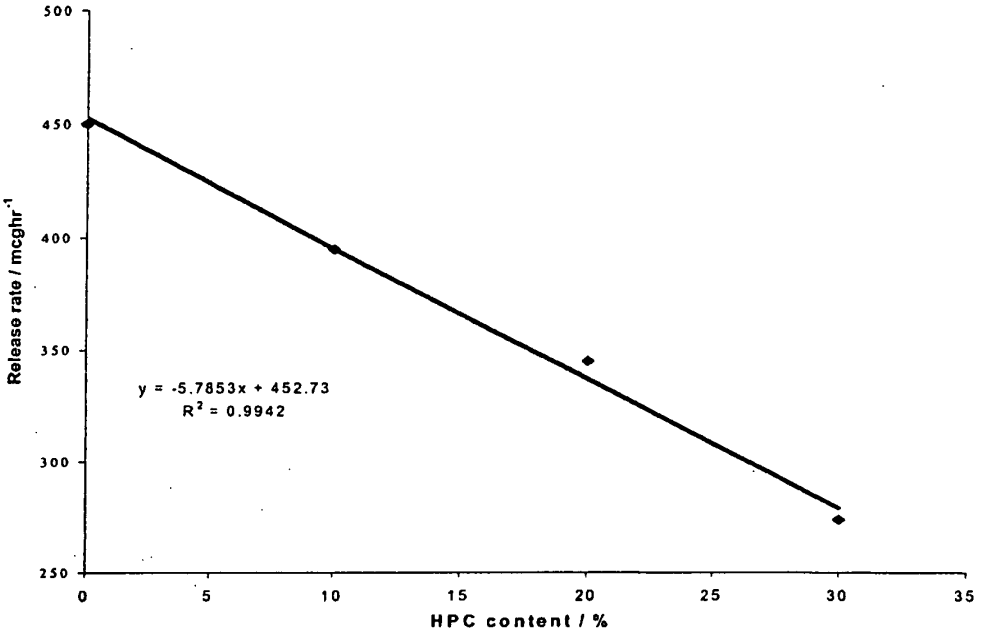


Figure 10. Demonstration of the linear relationship between NHT release rates and HPC content of nicotine buccal adhesive tablets using diffusion dissolution apparatus.

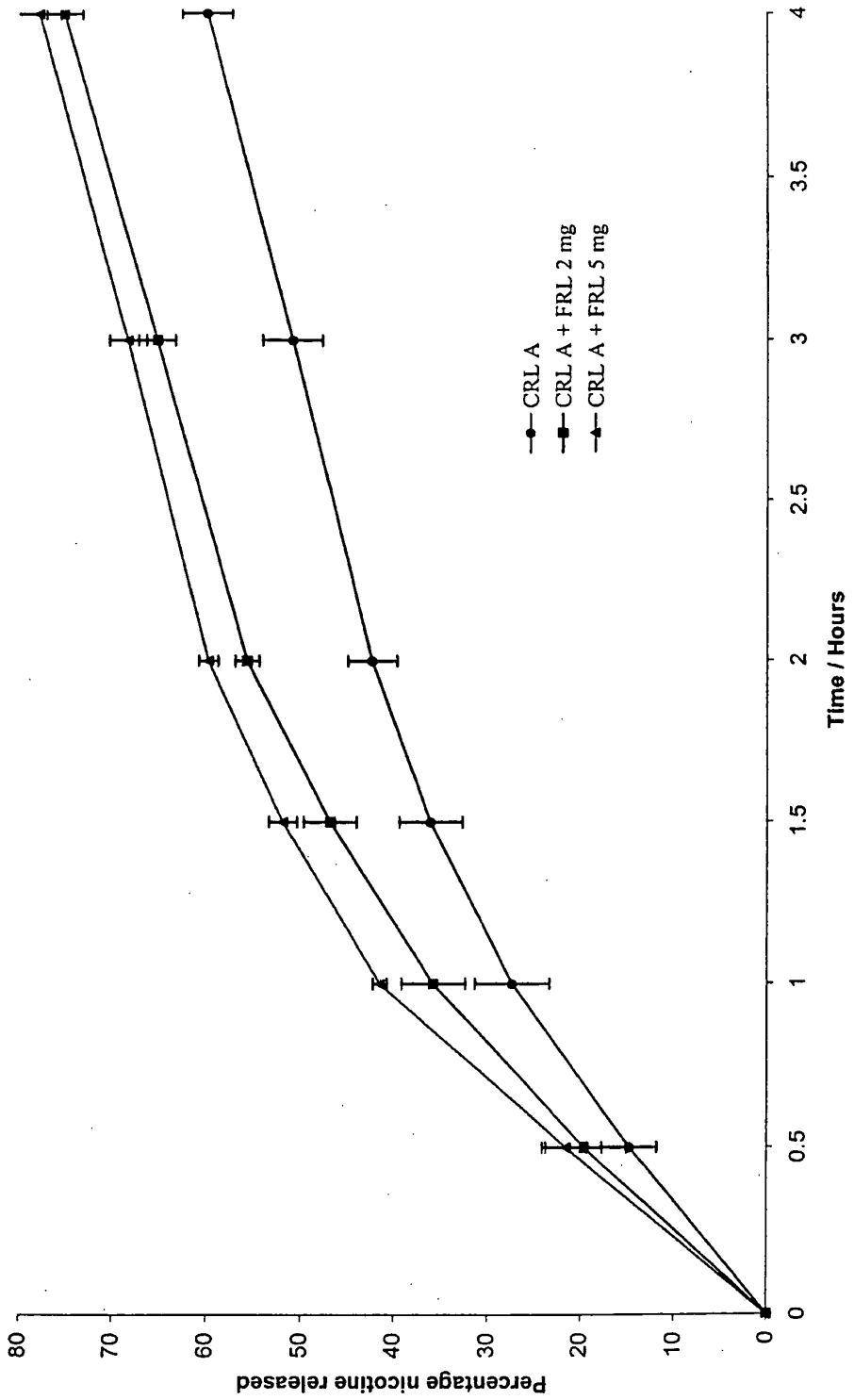

Percentage nicotine released
Time / Hours
CRL A
CRL A + FRL 2 mg
CRL A + FRL 5 mg
0
10
20
30
40
50
60
70
80
0
0.5
1
1.5
2
2.5
3
3.5
4

Fig 11

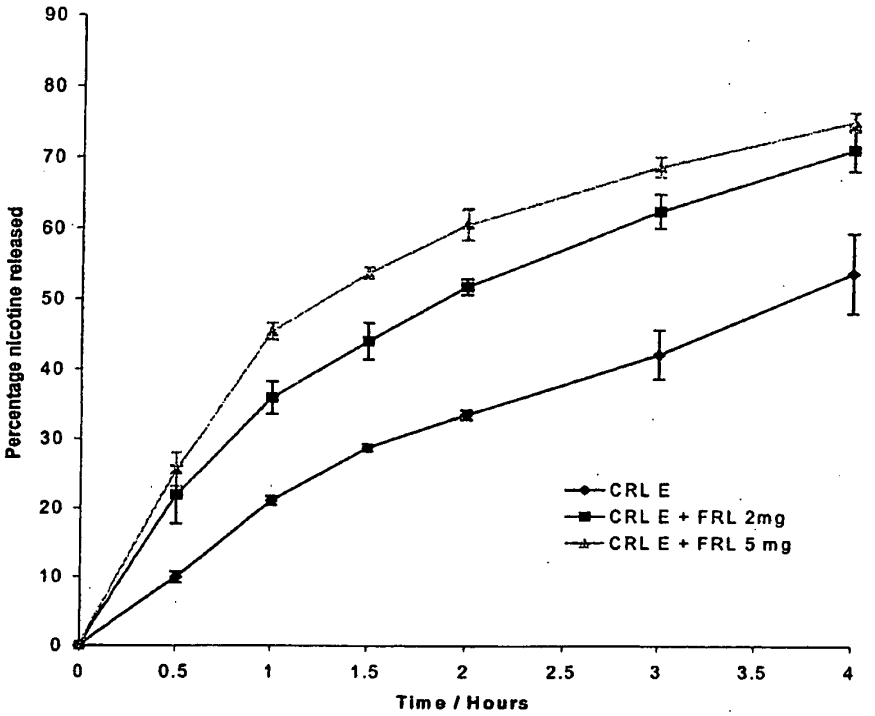


Figure 12. Dissolution profiles for formulation E and bilayer tablets consisting of formulation E and 2 mg and 5mg NHT fast release layers.

Figure 13. Drug release profiles of NHT bilayer tablets over the first hour of a 4 hour flow through dissolution test.

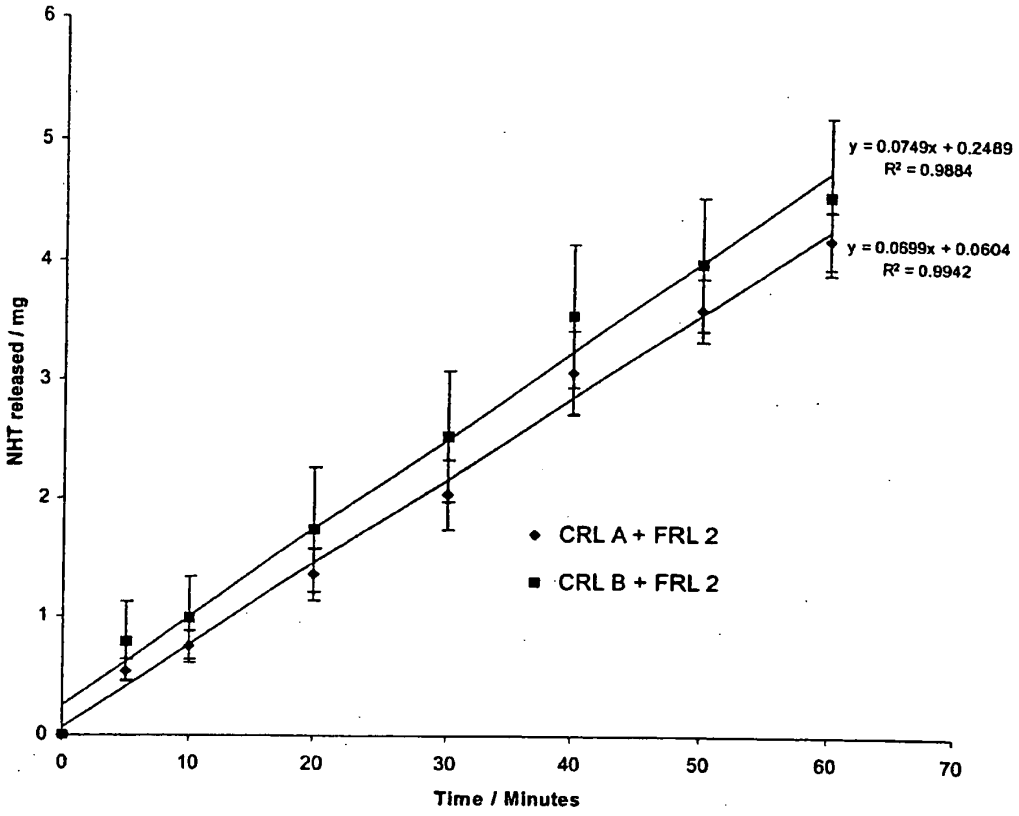


fig 13

INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 00/04428

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/24 A61K31/465

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 879 710 A (BROMET NORBERT E) 9 March 1999 (1999-03-09) column 1, line 12 - line 21 column 3, line 58 -column 4, line 2 column 4, line 33 - line 37 column 4, line 50 -column 5, line 5; claims 1,2,6; example 1; tables 1,2 --- -/--	1-8, 12-14, 16-23, 25, 27-33,36

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 February 2001	12/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Marttin, E

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 00/04428

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	LEE Y ET AL: "Oral mucosa controlled delivery of LHRH by bilayer mucoadhesive polymer systems" JOURNAL OF CONTROLLED RELEASE,NL,ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, vol. 37, no. 3, 1 December 1995 (1995-12-01), pages 251-261, XP004037428 ISSN: 0168-3659 page 252, left-hand column, line 4 - line 31 page 252, right-hand column, last paragraph; table 1 page 253, right-hand column, last paragraph -page 254, left-hand column, paragraph 1 page 254, left-hand column, last paragraph -page 255, right-hand column, paragraph 1; figure 2 page 260, line R, paragraph 2 ---	1-7,10, 12-14, 16-23, 25, 27-32, 35,36
X	US 5 236 713 A (WATO TAKAHIKO ET AL) 17 August 1993 (1993-08-17) column 2, line 18 - line 24 column 2, line 34 - line 48 column 3, line 13 - line 41 column 3, line 54 - line 59 column 3, line 37 -column 4, line 25; claims; examples ---	1-8, 12-14, 16-23, 25, 27-33,36
X	WO 98 46235 A (FIERUS MONIKA ;NEUSER DIETER (DE); BAYER AG (DE); WIEHL WOLFGANG () 22 October 1998 (1998-10-22) page 1, paragraph 1 page 1, paragraph 3 - paragraph 4 page 3, last paragraph -page 4, paragraph 1; claims; examples ---	1-3, 10-13, 15, 17-19, 21, 24-26, 35,36
A	WO 92 01445 A (ALZA CORP) 6 February 1992 (1992-02-06) page 5, paragraph 1 - paragraph 4 page 5, last paragraph -page 6, paragraph 2 page 6, last paragraph -page 7, line 1; claims 1,2,9,12,13,18-20; figures 1,5; examples --- -/--	1-36

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I. national Application No
PCT/GB 00/04428

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 13662 A (HENNINGFIELD JACK E ;CONE EDWARD J (US); JSR LLC (US); PINNEY JOHN) 16 March 2000 (2000-03-16) page 6, last paragraph -page 7, line 1 page 71, line 21 -page 8, line 14 page 9, line 20 - line 26 page 9, line 29 -page 10, line 25; figures page 16, line 8 - line 29 page 24, line 12 -page 25, line 29; claims; examples	1-3,7,9, 10,17, 18,34
T	PARK C R ET AL: "Formulation of a bilayer buccal adhesive tablet for nicotine replacement therapy." JOURNAL OF PHARMACY AND PHARMACOLOGY, vol. 52, no. Supplement, September 2000 (2000-09), page 303 XP000982579 137th British Pharmaceutical Conference;Birmingham, England, UK; September 10-13, 2000 ISSN: 0022-3573 the whole document	1-36

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
PCT/GB 00/04428

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5879710 A	09-03-1999	FR 2718020 A	06-10-1995
		AT 186210 T	15-11-1999
		CA 2186863 A	12-10-1995
		DE 69513157 D	09-12-1999
		EP 0754033 A	22-01-1997
		WO 9526713 A	12-10-1995
		JP 9510986 T	04-11-1997
US 5236713 A	17-08-1993	JP 1110622 A	27-04-1989
		JP 2573969 B	22-01-1997
WO 9846235 A	22-10-1998	DE 19715594 A	22-10-1998
		AU 7428698 A	11-11-1998
		BR 9808875 A	11-07-2000
		CN 1252725 T	10-05-2000
		EP 0979087 A	16-02-2000
		NO 994663 A	24-09-1999
		PL 336154 A	05-06-2000
		TR 9902396 T	21-01-2000
WO 9201445 A	06-02-1992	AT 111351 T	15-09-1994
		AU 652952 B	15-09-1994
		AU 8292491 A	18-02-1992
		CA 2047418 A	24-01-1992
		DE 69104045 D	20-10-1994
		DE 69104045 T	02-02-1995
		DK 540623 T	20-03-1995
		EP 0540623 A	12-05-1993
		ES 2064117 T	16-01-1995
		FI 930272 A	22-01-1993
		IE 912517 A,B	29-01-1992
		JP 6502622 T	24-03-1994
		MX 9100277 A	28-02-1992
		NO 930134 A	21-01-1993
		NZ 239033 A	27-04-1994
		PT 98374 A	31-01-1994
		US 5147654 A	15-09-1992
		ZA 9105648 A	27-05-1992
WO 0013662 A	16-03-2000	AU 5906899 A	27-03-2000
		AU 6412299 A	26-04-2000
		WO 0019977 A	13-04-2000